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Vitamin D and Pregnancy Loss: Biological Plausibility, Clinical Evidence and Current Controversies

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Abstract

Introduction: Vitamin D, beyond its classical role in calcium homeostasis and bone metabolism, exerts immunomodulatory and paracrine effects in reproductive tissues. Emerging evidence suggests a potential link between maternal vitamin D deficiency and miscarriage, particularly recurrent pregnancy loss (RPL). This review critically evaluates the biological plausibility and clinical evidence underlying this association.

Material and Methods: A structured literature search was performed in PubMed/MEDLINE, Embase, and Cochrane Library up to March 2026 using terms related to vitamin D and miscarriage. Eligible studies included human observational studies, interventional trials, and Mendelian randomization (MR) analyses assessing maternal 25-hydroxyvitamin D (25(OH)D) levels or supplementation in relation to miscarriage or RPL. Data extracted encompassed study design, population, vitamin D assessment, intervention, and pregnancy outcomes. Ten primary studies were included in the review, along with relevant meta-analyses and systematic reviews.

Results: Observational studies consistently report that low maternal 25(OH)D levels are associated with an increased risk of first-trimester miscarriage and RPL. Meta-analyses and umbrella reviews confirm these associations but highlight significant heterogeneity. MR studies do not support a direct causal effect of low vitamin D on miscarriage risk, suggesting that deficiency may be a marker of other risk factors (38). Interventional trials in high-risk women demonstrate that vitamin D supplementation improves immunologic profiles (Treg/Th17 balance, IL-23, IFN- γ) and may reduce miscarriage rates. Mechanistic studies reveal that vitamin D influences trophoblast function, endometrial receptivity, and maternal immune tolerance via the VDR/CYP27B1 pathway and HOXA10 expression.

Conclusions: Vitamin D deficiency is prevalent among women experiencing miscarriage, particularly

in early pregnancy and RPL. Evidence supports a biologically plausible immunomodulatory mechanism. While supplementation shows potential benefit in high-risk populations, routine vitamin D supplementation for miscarriage prevention cannot yet be universally recommended. Future large-scale, well-powered clinical trials are warranted to define optimal dosing, timing, and target populations.

Keywords: Vitamin D, Pregnancy, Recurrent Pregnancy Loss, Miscarriage

Introduction

Vitamin D is a fat-soluble secosteroid traditionally recognized for its role in calcium and phosphorus homeostasis, and bone metabolism (1,2). Endogenously, vitamin D is synthesized in the skin under ultraviolet B (UVB) radiation, while dietary intake and supplements provide an exogenous source. After hepatic conversion to 25-hydroxyvitamin D [25(OH)D], the main circulating form, it is hydroxylated in the kidneys to the biologically active 1,25-dihydroxyvitamin D [1,25(OH)₂D], which binds to vitamin D receptors (VDRs) expressed in multiple tissues, including ovarian and endometrial cells (1,3).

Vitamin D influences female reproductive function by regulating ovarian steroidogenesis, endometrial receptivity, and local immune tolerance, processes critical for successful implantation and early pregnancy maintenance (3–5). Miscarriage, defined as spontaneous pregnancy loss before fetal viability, affects 10–15% of recognized pregnancies globally, with most losses occurring in the first trimester. Recurrent pregnancy loss (RPL), generally defined as two or more consecutive miscarriages, affects a subset of women and carries significant physical and psychological burdens (6–8).

Observational studies suggest that low maternal 25(OH)D levels are associated with increased miscarriage risk, particularly in early pregnancy and among women with RPL (9–11). However, evidence remains heterogeneous, with Mendelian randomization studies indicating that low vitamin D may be a marker rather than a causal factor, reflecting con-

found variables such as maternal BMI, lifestyle, and supplement use (12). Mechanistic evidence supports a biologically plausible role of vitamin D in early pregnancy via modulation of trophoblast invasion, spiral artery remodeling, and local immunomodulation through T-regulatory cells and the VDR/CYP27B1 pathway in the endometrium and placenta (13,14).

This narrative review synthesizes current evidence on vitamin D and miscarriage, highlighting underlying biological mechanisms, observational and interventional study findings, and potential clinical implications for preconception and early pregnancy management.

Methods

A structured literature search was conducted to identify studies investigating maternal vitamin D status and pregnancy loss. Searches were performed in PubMed/MEDLINE, Embase, and Cochrane Library, including publications up to March 2026. Search terms included "vitamin D" OR "25-hydroxyvitamin D" OR "cholecalciferol" AND "miscarriage" OR "spontaneous abortion" OR "early pregnancy loss" OR "recurrent pregnancy loss".

Eligible studies were human observational studies (cohort, case-control, cross-sectional) and interventional trials evaluating vitamin D levels, supplementation, or genetic predisposition (Mendelian randomization) in relation to miscarriage or RPL. Systematic reviews and meta-analyses were screened for

additional relevant studies. Exclusion criteria included animal studies, case reports, and studies addressing infertility without pregnancy outcomes.

The resulted studies of the aforementioned search strategy included 10 primary studies, along with several meta-analyses and systematic reviews addressing vitamin D deficiency and miscarriage risk (9,10,11,12,14,15,16,17,18,19).

Two reviewers independently screened titles and abstracts, followed by full-text assessment. Extracted data included study design, sample size, population characteristics, vitamin D measurement method, thresholds for deficiency, interventions, outcomes, and effect estimates. Discrepancies were resolved by consensus. This approach allowed a comprehensive synthesis of mechanistic, observational, and interventional evidence linking vitamin D to miscarriage risk. A summary of the design, population characteristics, vitamin D assessment, interventions and main findings of the included studies is presented in Table 1.

Clinical Evidence: Vitamin D and Miscarriage

Observational Evidence

Observational studies have consistently examined the association between maternal 25-hydroxyvitamin D (25(OH)D) levels and pregnancy outcomes, particularly miscarriage and recurrent pregnancy loss (RPL). Tamblyn et al. (2022) conducted a systematic review and meta-analysis of 10 studies including 7,663 women, finding that vitamin D deficiency (<50 nmol/L) was associated with a significantly higher risk of miscarriage compared with adequate vitamin D levels (>75 nmol/L), with a dose-response relationship indicating greater risk at lower 25(OH)D concentrations (9). This meta-analysis highlighted substantial heterogeneity among studies in terms of

measurement methods, population characteristics, and definitions of deficiency.

A prospective cohort study in Denmark, the Odense Child Cohort, involving 1,683 women, reported that first-trimester 25(OH)D insufficiency (<50 nmol/L) was associated with a two- to three-fold increased risk of early miscarriage. Interestingly, this association was limited to losses occurring in the first trimester, supporting the biological importance of vitamin D during early implantation and placentation (10).

Ko et al. (2024) examined 371 women presenting with first-trimester threatened miscarriage and reported no overall difference in miscarriage rates between vitamin D deficient and sufficient women. However, in those presenting with bleeding before 6 weeks, miscarriage rates were paradoxically higher among women with sufficient vitamin D, suggesting that other factors such as inflammation or supplementation may modulate outcomes in this subgroup (15).

Similarly, Subramanian et al. (2022) measured preconception 25(OH)D levels in 362 women attempting conception and found no statistically significant association with miscarriage, indicating that in low-risk populations, vitamin D deficiency may not be the primary driver of early pregnancy loss (16).

An observational case-control study in Iraqi women by Kasim (2022) included 40 women with miscarriage and 40 controls, showing that 95% of women in the miscarriage group were vitamin D deficient compared to 17.5% of controls, reinforcing the high prevalence of deficiency in women experiencing pregnancy loss (11).

Mendelian Randomization Studies

Mendelian randomization (MR) offers a method to infer causality while reducing confounding. Zhang et al. (2024) used UK Biobank data to examine genetic variants associated with lifelong differences in 25(OH)D levels and their relationship to miscarriage. The MR study found no evidence supporting a causal

Table 1. Summary table.

Study/Year	Design	Population/ Sample Size	Vitamin D Measure/ Threshold	Intervention	Main Outcomes/ Findings	Ref #
Tamblin JA et al., 2022	Systematic Review & Meta-analysis	7,663 women across 10 studies	<50 nmol/L = deficient; >75 nmol/L = sufficient	None	Vitamin D deficiency associated with increased miscarriage risk; dose-response effect	9
Andersen LB et al., 2015 (Odense Child Cohort)	Prospective cohort	1,683 pregnant women	25(OH)D <50 nmol/L = insufficiency	None	First-trimester insufficiency associated with 2–3x increased miscarriage risk	10
Ko JKY et al., 2024	Prospective cohort	371 women with first-trimester threatened miscarriage	25(OH)D deficiency vs sufficient	None	Overall, no difference in miscarriage; higher risk in early bleeding with sufficient vitamin D	15
Subramanian A et al., 2022	Prospective cohort (preconception)	362 women attempting conception	25(OH)D measured preconception	None	No significant association with miscarriage in low-risk population	16
Chien MC et al., 2024	Umbrella review/ Systematic review	>250,000 women across meta-analyses	Not applicable	None	Vitamin D deficiency associated with miscarriage and adverse pregnancy outcomes; evidence heterogeneous	17
Kasim SF, 2022	Case-control	80 women (40 miscarriage, 40 controls)	25(OH)D deficiency	None	95% of miscarriage group deficient vs 17.5% controls; strong correlation	11
Zhang F et al., 2024	Mendelian Randomization	UK Biobank (thousands of women)	Genetic proxies for lifelong low 25(OH)D	None	No causal effect of low vitamin D on miscarriage risk	12
Ji J et al., 2019	Mechanistic/ Immunologic	Women with RPL	25(OH)D measured	None	Vitamin D regulates Treg/Th17 balance, improves immune tolerance	14
Ibrahim ZM et al., 2013	Randomized Controlled Trial	Women with RPL	25(OH)D measured	0.25 µg vitamin D ₃ twice daily	Decreased IFN-γ; improved immune tolerance; non-significant reduction in miscarriage	18
Samimi M et al., 2017	Double-blind RCT	Women with unexplained RPL	25(OH)D measured	400 IU vitamin D ₃ daily	Miscarriage rate reduced 12.8% vs 34.2%; IL-23 levels reduced	19

effect of genetically determined low vitamin D on miscarriage risk, suggesting that observational associations may be influenced by confounding variables such as maternal BMI, lifestyle factors, or supplement use (12).

This finding contrasts with the positive associations observed in conventional cohort studies, emphasizing the need for careful interpretation and highlighting the complexity of vitamin D's role in reproductive outcomes.

Systematic Reviews and Umbrella Analyses

Chien et al. (2024) performed an umbrella review of systematic reviews and meta-analyses including over 250,000 women, confirming that vitamin D deficiency is associated with increased risks of miscarriage, preeclampsia, preterm birth, and gestational diabetes. The strength of evidence for miscarriage was less robust due to methodological heterogeneity and variable thresholds for deficiency, but the review supports the concept that vitamin D contributes to early pregnancy success through immune, endocrine, and placental mechanisms (17).

Tamblyn et al. (2022), in the previously mentioned meta-analysis, emphasized that women with severe deficiency (<30 nmol/L) had the highest risk of miscarriage, suggesting a threshold effect. This aligns with recommendations that maintaining 25(OH)D levels above 50 nmol/L is minimally required for optimal reproductive outcomes, with higher targets potentially beneficial in high-risk groups (9).

Interventional Trials

Interventional data examining vitamin D supplementation for miscarriage prevention are limited but suggest potential benefits in high-risk populations.

Samimi et al. (2017) conducted a double-blind randomized controlled trial (RCT) in women with unexplained recurrent spontaneous abortion. Par-

ticipants received 400 IU vitamin D₃ daily versus placebo. The miscarriage rate was significantly lower in the intervention group (12.8%) compared to controls (34.2%), and IL-23 levels were reduced, indicating immunomodulatory effects of supplementation (19).

Ibrahim et al. (2013) evaluated 0.25 µg vitamin D₃ twice daily in women with RPL and observed decreased IFN-γ levels, suggesting improved immune tolerance, although the reduction in miscarriage risk did not reach statistical significance (18). These findings point to potential mechanistic benefits even when clinical outcomes are not conclusive.

Rafiee et al. (2015) administered high-dose vitamin D₃ (300,000 IU) to women with RPL and reported decreased Th17 cell numbers and a lower Th17/Treg ratio, further demonstrating the immunoregulatory role of vitamin D in early pregnancy (20).

These trials, while promising, are limited by small sample sizes, heterogeneity in dosing, and differences in baseline deficiency levels. Nevertheless, they provide mechanistic and preliminary clinical evidence supporting vitamin D supplementation in selected high-risk women.

Integration of Evidence

Overall, the evidence from observational studies, systematic reviews, and interventional trials suggests a consistent pattern: vitamin D deficiency is common among women with early miscarriage or RPL, and low 25(OH)D levels correlate with increased risk, particularly in early gestation. Mechanistic studies provide a plausible biological basis through immune modulation, endometrial receptivity, and trophoblast function. However, MR studies indicate that deficiency may act as a marker rather than a causal factor, underscoring the complexity of the vitamin D–miscarriage relationship (12).

The strongest clinical signal is observed in high-risk populations, including women with prior RPL,

limited sun exposure, high BMI, or chronic inflammatory conditions. These findings suggest a targeted approach for screening and supplementation may be beneficial, pending confirmation in larger, well-powered RCTs (9,10,14,18,19,21).

Biological Plausibility and Mechanisms of Vitamin D in Miscarriage

Vitamin D is increasingly recognized as a multifunctional hormone that extends beyond calcium and bone metabolism, influencing immune, endocrine, and reproductive systems. Mechanistic studies provide a biologically plausible explanation for the observed associations between low maternal 25-hydroxyvitamin D (25(OH)D) levels and miscarriage risk, particularly in early pregnancy and recurrent pregnancy loss (RPL). These mechanisms involve local intracrine activation, modulation of the maternal-fetal immune interface, regulation of trophoblast function, and control of endometrial receptivity (1,13,14,22).

Local Activation of Vitamin D in Reproductive Tissues

Maternal decidua and placental trophoblasts express both the vitamin D receptor (VDR) and the enzyme CYP27B1, which converts circulating 25(OH)D into its biologically active form, 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$) (13). This intracrine pathway allows localized regulation of gene expression, independent of circulating calcitriol levels. Active vitamin D in the endometrium and placenta modulates genes involved in immune tolerance, angiogenesis, and cellular differentiation, directly influencing implantation success and early placental development (13,14).

Immunomodulatory Effects

A central component of early pregnancy maintenance

is immune tolerance, allowing maternal acceptance of the semi-allogenic fetus. Vitamin D contributes to this process through several mechanisms:

- Regulatory T cells (Tregs): Vitamin D enhances the differentiation and proliferation of Tregs, which suppress excessive maternal immune activation against fetal antigens (14,18).

- Th17 cells: Vitamin D downregulates pro-inflammatory Th17 cells and reduces the Th17/Treg ratio, decreasing local inflammation and improving implantation success (14,18).

- Cytokine modulation: Supplementation studies show reduced levels of inflammatory cytokines such as IFN- γ and IL-23 in women with RPL, correlating with improved pregnancy outcomes (18,19).

These immunomodulatory effects create a more tolerant maternal immune environment conducive to early placentation.

Regulation of Endometrial Receptivity

Vitamin D influences endometrial receptivity through molecular regulation of key implantation-related genes. One critical target is HOXA10, a transcription factor necessary for proper decidualization and embryo implantation. Experimental data suggest that vitamin D deficiency reduces HOXA10 expression, potentially impairing endometrial differentiation and the capacity to support embryo implantation (13).

In addition, CYP27B1 activity within the endometrium ensures adequate local production of $1,25(\text{OH})_2\text{D}$, which synergizes with VDR to regulate other genes involved in adhesion, extracellular matrix remodeling, and angiogenesis. These processes are essential for the formation of a functional maternal-fetal interface (13,14).

Trophoblast Function and Placental Development

Vitamin D impacts trophoblast proliferation, invasion, and differentiation, critical for early placental

formation. Local calcitriol modulates expression of angiogenic factors, supporting spiral artery remodeling and ensuring adequate perfusion of the developing placenta. Deficiency in vitamin D may impair trophoblast invasion and vascular remodeling, contributing to early pregnancy loss or suboptimal placentation (13,14).

Furthermore, VDR activation in trophoblasts enhances production of anti-inflammatory mediators and promotes tolerance at the maternal-fetal interface, reducing the likelihood of immune-mediated miscarriage (14).

Integration of Mechanistic Pathways

Collectively, these pathways illustrate a biologically coherent model linking vitamin D to early pregnancy maintenance:

1. Circulating 25(OH)D enters decidual and placental tissue.
2. Local CYP27B1 converts 25(OH)D to 1,25(OH)₂D, activating VDR.
3. VDR-mediated transcription regulates Treg/Th17 balance, anti-inflammatory cytokine production, and trophoblast-related genes.
4. HOXA10 expression and endometrial differentiation are optimized, supporting embryo implantation.
5. Placental angiogenesis and trophoblast invasion proceed effectively, minimizing the risk of early pregnancy loss (13,14).

This mechanistic framework aligns with observational and interventional findings: vitamin D deficiency is most strongly associated with first-trimester miscarriage and RPL, while supplementation can restore immunologic balance and potentially improve early pregnancy outcomes (9,10,14,15,16,18,19,21).

Clinical and Research Implications

Understanding these mechanisms emphasizes that vitamin D is not merely a nutritional factor but

a local regulator of reproductive physiology. This provides a rationale for preconception or early pregnancy assessment of vitamin D status in women at high risk of miscarriage. However, the interplay between genetic predisposition, environmental factors, and lifestyle remains complex, and MR studies indicate that deficiency may be an associated risk marker rather than a direct causal factor (12).

Future research should focus on elucidating optimal supplementation strategies (dose, timing, target populations) and validating mechanistic biomarkers (e.g., HOXA10, Treg/Th17 ratio) in clinical trials to improve individualized reproductive care (13,14).

Clinical Implications

The mechanistic and clinical evidence reviewed suggests that vitamin D plays a role in early pregnancy maintenance through immunomodulation, endometrial receptivity, and trophoblast function (13,14). Women with low 25-hydroxyvitamin D (25(OH)D) levels, particularly during the first trimester or preconception, appear to have an increased risk of miscarriage and recurrent pregnancy loss (RPL) (9-11). Screening for vitamin D deficiency in women with a history of miscarriage, high body mass index, limited sun exposure, or other risk factors may help identify individuals who could benefit from supplementation (9-11).

Vitamin D supplementation is safe, cost-effective, and widely accessible. Randomized trials in women with RPL demonstrate that supplementation can improve immunologic parameters, such as increasing regulatory T cells, decreasing pro-inflammatory cytokines, and improving the Th17/Treg ratio, potentially reducing miscarriage risk (14,18,19). Observational and interventional data indicate that maintaining 25(OH)D levels above 50 nmol/L (20 ng/mL) is associated with more favorable pregnancy outcomes, while higher targets (75 nmol/L or 30

ng/mL) may be considered in high-risk populations (9,10,16).

Despite these promising findings, routine supplementation solely for miscarriage prevention cannot yet be universally recommended. Evidence is limited by small sample sizes, heterogeneity in dosing protocols, and variability in study populations (18,19). Clinicians should adopt an individualized approach, integrating vitamin D assessment into preconception counseling or early pregnancy care for women at risk, while considering other established interventions for miscarriage prevention (9,14).

Future research should focus on well-designed, adequately powered randomized controlled trials to determine optimal dosing, timing, and target populations, and to confirm whether vitamin D supplementation can meaningfully reduce miscarriage risk. Until robust clinical evidence is available, correction of deficiency in high-risk women represents a pragmatic strategy with potential benefit and minimal risk, aligning with broader reproductive health and prenatal care recommendations (9,14,18,19).

Controversies and Future Research

Despite extensive research, the relationship between vitamin D status and miscarriage remains complex and sometimes contradictory. Observational studies consistently report associations between low maternal 25-hydroxyvitamin D (25(OH)D) levels and increased risk of early pregnancy loss or recurrent pregnancy loss (RPL) (9-11). However, heterogeneity in these studies -including differences in population characteristics, vitamin D thresholds, timing of measurement, and adjustment for confounders -complicates interpretation. Some prospective cohorts and preconception studies fail to demonstrate a statistically significant association, suggesting that low vitamin D may be a marker of general reproductive or systemic health rather than

a causal factor (12,15,16).

Mendelian randomization (MR) studies, designed to minimize confounding and reverse causation, have not supported a causal relationship between genetically determined low vitamin D and miscarriage risk (12). These findings highlight the possibility that observational associations are influenced by unmeasured variables such as obesity, inflammation, lifestyle factors, and supplement use. Consequently, it remains uncertain whether vitamin D deficiency is directly etiologic or simply associated with a milieu that predisposes to early pregnancy loss.

Interventional studies provide preliminary evidence that vitamin D supplementation may improve immunologic parameters and pregnancy outcomes in high-risk women with RPL (18,19). Nevertheless, existing trials are limited by small sample sizes, variable doses and forms of vitamin D, and inconsistent outcome definitions. The optimal dose, timing, and target population for supplementation remain undefined, and no standardized international guidelines exist specifically for miscarriage prevention.

Future research should address these gaps with large, multicenter, randomized controlled trials assessing preconception and early pregnancy vitamin D supplementation in women with a history of miscarriage or at high risk. Studies should stratify participants by baseline vitamin D status, BMI, ethnicity, and genetic background, and include mechanistic biomarkers such as Treg/Th17 ratios and HOXA10 expression to link biological effects with clinical outcomes (13,14).

Additionally, standardized definitions of deficiency, consistent thresholds for supplementation, and uniform outcome measures are critical to improve comparability across studies. Clarifying these controversies will allow evidence-based recommendations for integrating vitamin D evaluation and supplementation into reproductive care, potentially improving early pregnancy outcomes in at-risk pop-

ulations (9,10,14).

Conclusions

Vitamin D, beyond its established role in bone and calcium metabolism, appears to influence key processes in early pregnancy, including endometrial receptivity, placental development, and maternal immune tolerance. Observational studies and meta-analyses consistently show that low maternal 25-hydroxyvitamin D (25(OH)D) levels are more prevalent among women experiencing miscarriage, particularly in the first trimester and in cases of recurrent pregnancy loss (RPL). Mechanistic studies support a biologically plausible role for vitamin D, demonstrating regulation of regulatory T cells, suppression of pro-inflammatory Th17 cells, modulation of HOXA10 expression, and local activation via CYP27B1 in decidual and placental tissues.

Interventional trials suggest that supplementation can improve immunologic profiles and reduce miscarriage risk in high-risk populations; however, evidence is limited by small sample sizes, heterogeneous dosing, and methodological variability. Routine supplementation solely for miscarriage prevention cannot yet be universally recommended.

Assessment and correction of vitamin D deficiency in women at high risk—such as those with RPL, limited sun exposure, or elevated BMI—represents a safe, low-cost, and potentially beneficial strategy. Future research should focus on well-powered randomized controlled trials to define optimal dosing, timing, and target populations, integrating mechanistic biomarkers to clarify causal pathways and establish evidence-based guidelines for reproductive care.

Author contributions

Conceptualization: D.P., G.F.G., A.D.; Literature search: D.P., N.R., T.K.; Data extraction and analysis:

D.P., P.T.; Writing—original draft preparation: D.P.; Writing—review and editing: N.R., T.K., A.D.; Supervision: G.F.G., A.D. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Ethics Approval

Not applicable, as this study is based on previously published data and does not involve human participants or animal subjects.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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